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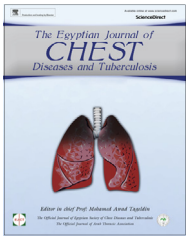

ORIGINAL ARTICLE

Study of blood desmosine level in patients with COPD exacerbation in relation to severity

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KEYWORDS

COPD;
Acute of exacerbation;
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Abstract *Background:* Desmosine (DES), a cross linking amino-acid unique to mature elastin is expected to increase in proportion to the recruitment and activation of the inflammatory cells induced by smoking, exposure to biomass fuel smoke etc., or during acute exacerbations of COPD. Therefore, it could be investigated as a biomarker of the stable disease and during exacerbations.

Aim of the study: The study aimed to evaluate blood DES level in COPD exacerbation as well as in the stable state, and to assess its relation to severity of exacerbation.

Methods: The study included 20 COPD patients and 20 healthy controls all individuals were subjected to chest radiograph, spirometric pulmonary function, arterial oxygen saturation ($SapO_2$), arterial blood gases (ABG, patients only), and ELISA – based blood DES level assay which was done once in controls and twice – in COPD patients, both during exacerbation and one month later after being stable.

Results: DES level was more elevated, with high statistical significance, in COPD patients (both during exacerbation and in the stable state) compared to the control subjects, as well as it was significantly higher in COPD patients during exacerbation than in the same patients' group after being stable. The DES level showed significant negative correlation with FEV_1% in stable COPD and significant positive correlation with the severity of COPD exacerbation.

Conclusion: Blood DES level as a marker of elastin degradation was elevated in stable COPD with more rise during exacerbation indicating that exacerbations could add more lung destruction leading to further deterioration of the lung function.

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Introduction and rationale

Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease is characterized by airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles and gases. Exacerbations and

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Table 1 Age and sex distribution among both COPD patients' and control groups.

		Patients' group (n = 20)		Control group (n = 20)		P-value
Age (years)	Mean ± SD	66.4 ± 11.2		59.3 ± 13.6		0.07 (NS)
	Range	48–92		45–73		
Sex	Male	17	85%	15	75%	0.7 (NS)
	Female	3	15%	5	25%	
Smoking index (pack year)	Mean ± SD	55.6 ± 23.7		10.1 ± 4.2		< 0.001 (HS)

NS: no statistically significant difference.

Table 2 Shows relationship between blood desmosine and smoking status during acute exacerbation of COPD in patients' group.

	During exacerbation		P value
	Current smoker (N = 9)	Ex-smoker (N = 11)	
Blood desmosine (ng/ml) Mean ± SD	0.88 ± 0.284	0.67 ± 0.328	0.1 (NS)

NS: no statistically significant difference.

Table 4 Correlation between blood desmosine level and some clinical laboratory and spirometric characteristics in COPD patients' group.

	Blood desmosine	
	R	P-value
Age (years)	−0.1	0.6 (NS)
BAP-65 score	0.58	0.007*
FEV_1% of predicted	−0.82	0.0001*
FVC% of predicted	−0.79	0.0001*
FEV_1/FVC%	−0.72	0.001*
COPD stage	0.72	0.001*

NS: No statistically significant difference.
* Statistically highly significant difference.

comorbidities contribute to the overall severity in individual patients [1].

The course of COPD is characterized by progressive lung function decline and exacerbations leading to physiologic deterioration and respiratory failure especially at advanced stages of the disease [2]. An exacerbation of COPD is defined as an acute event characterized by a worsening of the patient's respiratory symptoms beyond normal day to day variations and leads to a change in medication.

The best predictor of having frequent exacerbations (i.e. greater than or equal to 2years) is a history of previously treated events; the risk of exacerbations also increases as the airflow limitation worsens [3].

Desmosine (DES) and Isodesmosine (IDES) are cross linking amino-acids unique to mature elastin, in conjunction with microfibrils formed from tropoelastin [4]. Blood normally contains fragments derived from tropoelastins and from degraded cross-linked mature elastin (i.e. DES and IDES) [4].

These particles are expected to increase both in the blood and urine in proportion to the recruitment and activation of the inflammatory cells particularly neutrophil induced by smoking, exposure to biomass fuel smoke etc., or during acute exacerbations of COPD. Therefore, they could be measured and examined as biomarkers of the stable disease and during exacerbations.

Aim of the study

The study aimed to evaluate blood desmosine level as a marker of elastinolysis in acute exacerbation of COPD as well as in the stable state of the disease, and to assess its relation to the severity of the exacerbation.

Subjects and methods

This case control and prospective study was conducted in the Chest Unit, Internal Medicine Department, Suez Canal University, Ismailia, Egypt. Two groups of participants were included in the study; the first group included 20 patients with COPD who were admitted through ER and chest clinic in acute exacerbation. All of them met the criteria of the Global Initiative for the Diagnosis of COPD (GOLD) [1]. Grading of severity of the exacerbation was done using the BAP-65 score [5] which included BUN level > 25 mg/dl, altered sensorium,

Table 3 Blood desmosine level among COPD patients' and control groups.

		Patients' group (exacerbation) (n = 20)	Patients' group (stable state) (n = 20)	Control group (n = 20)	P-value
Desmosine (ng/ml)	Mean ± SD	0.77 ± 0.32[a]	0.37 ± 0.29[b]	0.063 ± 0.068[c]	0.001*
	Range	0.2–1.6	0–1.2	0–0.2	

[a–c] Indicate statistically significant difference within groups (Bonferroni test).
* Statistically highly significant difference.

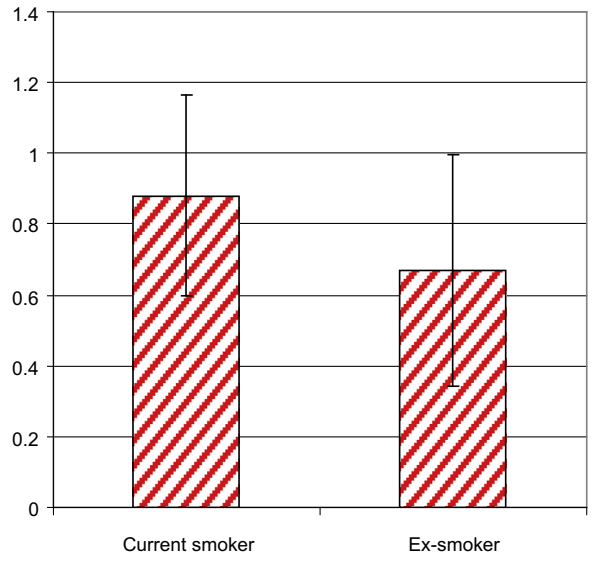

Figure 1 Shows non-significant higher blood desmosine level in current smokers than in ex-smokers in COPD patients during acute exacerbation.

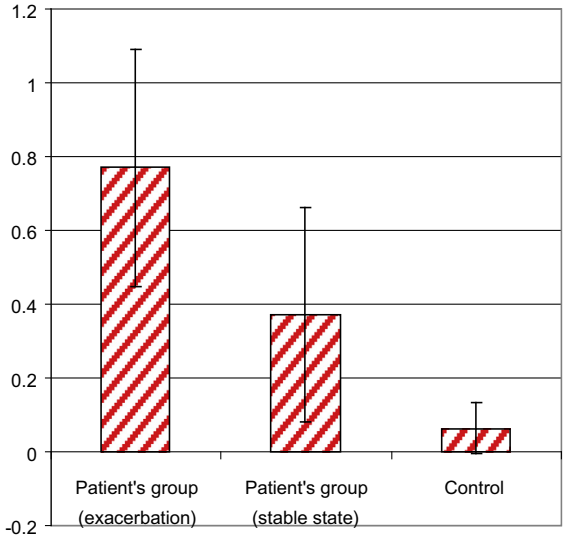

Figure 2 Shows significantly higher blood desmosine level (ng/ml) in COPD patients during exacerbation compared to the same group in the stable state. Patients' group, during both exacerbation and in the stable state, has highly significant, higher level compared to controls.

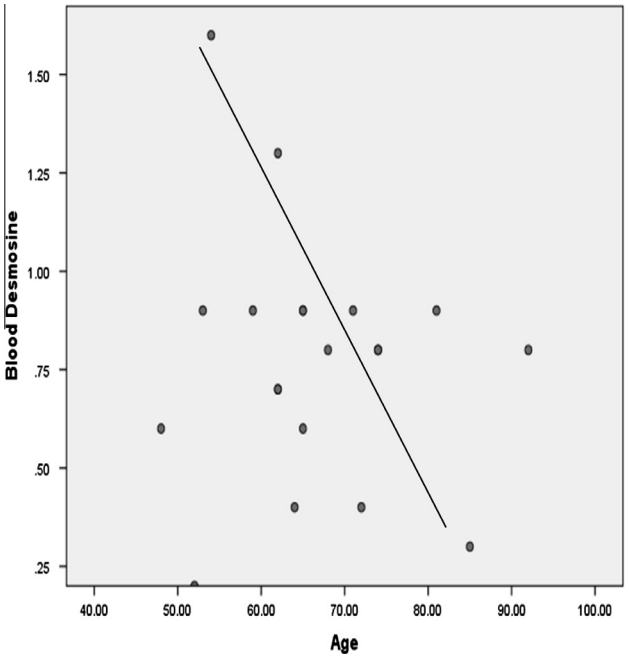

Figure 3 Shows non-significant negative correlation between blood desmosine (ng/ml) and age (years) in COPD patients.

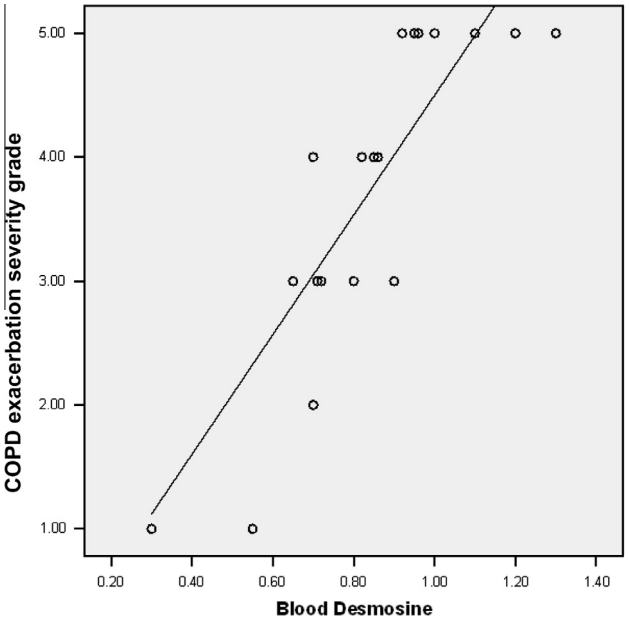

Figure 4 Shows highly significant positive correlation between blood desmosine (ng/ml) and grade of severity of COPD exacerbation based on BAP-65 score.

and pulse rate >109beats/min. Patients younger than 65 years were classified as grade 1, whereas those older than 65 years without other risk factors were classified as class 2. The designation into risk classes 3, 4, 5 was based on whether the patient had 1, 2 or 3 of the central risk factors respectively. The control group involved 20 healthy subjects who did not experience recent (within two weeks) chest infection.

The following subjects were excluded:

1) Age < 40 years.
2) Patients with history of pulmonary disease other than COPD.
3) Chronic kidney and heart diseases.

All individuals were subjected to the following; complete medical history and physical examination, frontal chest radio-

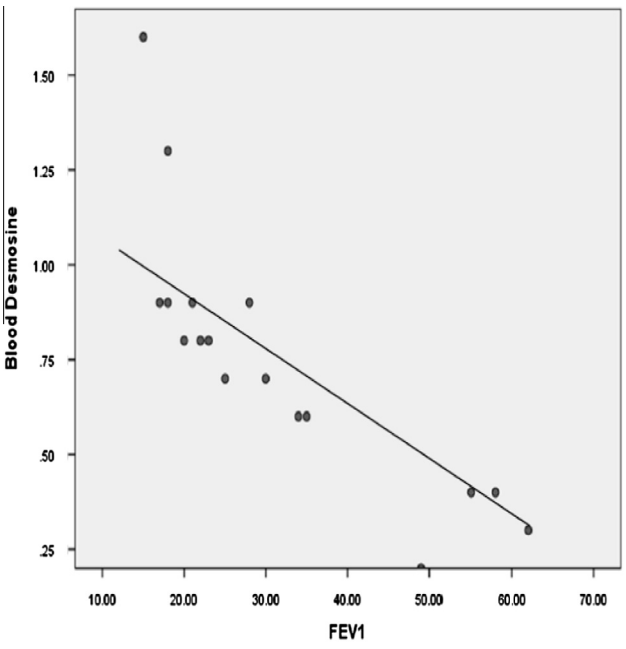

Figure 5 Shows highly significant negative correlation between blood desmosine (ng/ml) and FEV_1% of predicted in patients with COPD.

graph, ABG (patients group only), spirometric pulmonary function testing, routine blood work (CBC, S.creatinine, FBS, SGPT, etc.) and blood desmosine level which was also remeasured in the patients' group, one month after hospital discharge when they became stable. Blood desmosine assay employed the quantitative enzyme immune assay technique using a colorimetric method (i.e. the color intensity increases in proportion to the amount of desmosine) with a detection range: 0.156–10 ng/ml (MyBioSource, San Diego, U.S.A.), the minimum detectable level of human DES is <0.039 ng/ml.

Results

There are non-significant differences between patients and controls regarding sex and age with, highly significant, higher smoking index in patients with COPD.

Discussion

In the present study, the blood desmosine level was higher in COPD patients whether in the stable state (0.37 ng/ml ± 0.29) or during exacerbation (0.77 ng/ml ± 0.32) compared to control subjects (0.063 ng/ml ± 0.069) with highly significant difference ($p < 0.01$ (Table 3, Fig. 2). Our results were consistent with those of Attia et al. [6], who found a higher blood desmosine level in COPD patients than in control subjects, but with lower values than our values, especially during exacerbation (0.34 ng/ml ± 0.04) which could be explained by possible impaired urinary excretion in our patients causing more elevation of blood desmosine as 35% of our patients were in class V according to BAP-65 scoring for severity of exacerbation of COPD [5] i.e. they had elevated BUN among other risk factors. In the present study we did not concomitantly measure urinary desmosine so that the total desmosine level (blood and urine) would be more indicative of elastin turnover status. Huang et al. [7] found that the level was higher in only 40% of COPD patients during exacerbation and not in the stable state. Again these results are different from ours, and this could reflect the small sample size and the higher score of acute exacerbation severity in our studied patients' group.

The present study also disclosed significantly higher level of blood desmosine in patients' group during exacerbation (0.77 ng/ml ± 0.32) compared to the same group after being stable (0.37 ng/ml ± /dl) (Table 3, Fig. 2). These results are in keeping with those of Fiorenza et al. [8], who found a higher urinary desmosine concentration during acute exacerbation of COPD compared to the stable state in the same patients' group. These results suggest that COPD patients during acute exacerbation might have increased elastin degradation which results in more elastin-derived cross-linking amino acids (DES and IDES) than in patients with the stable disease. This probably reflects the increased number and activation of neutrophils within the lungs, occurring during an acute exacerbation of COPD [9,10], which are responsible for the purulence of the sputum and the high concentration of sputum serine proteases such as neutrophil elastase [11]. Thus, it may be supposed that the increased desmosine production in an exacerbation of COPD is the result of acute damage to elastin in airways and alveolar walls by neutrophil elastase, adding to the "baseline" elastin degradation found in the stable COPD [12]. Regarding the association between blood desmosine and FEV_1%, it had been found that FEV_1% negatively correlated with blood desmosine with statistically significant difference ($r = -0.82$ and $P < 0.05$) (Table 4, Fig. 5).

Previous studies, on the correlation between the desmosine and lung function, gave conflicting results. Huang et al. [6] did not observe a significant correlation between FEV_1% and blood DES in patients with the stable disease, or during an exacerbation of COPD. Gottlieb et al. [13], studied apparently healthy smoking adult males and found significantly higher desmosine production in rapid FEV_1 decliners than in slow decliners, and a significant correlation between desmosine production and the rate of FEV_1 decline over 6.3 years. In contrast, Boutin et al. [14], found significantly lower levels of desmosine production in COPD patients with rapid FEV_1 decline compared with slow decliners over 15 years. However, Attia et al. [6], found that the blood desmosine level was significantly but inversely correlated with FEV_1%. The inconsistent results of some studies could be explained by recruiting patients with different underlying pathology of COPD (i.e. predominantly chronic bronchitis and small airway disease rather than emphysema).

In this study, we also investigated the association between BAP-65 score [5] (Table 4, Fig. 4), that was used to grade the severity of acute exacerbation of COPD and it was found that there was statistically significant positive correlation between this score and blood DES level ($r = 0.58$ and $p < 0.05$), so blood DES can be used as a biomarker of the severity of acute exacerbation of COPD. However further studies on a larger number of patients are needed with assessment of the level in patients with the stable disease (i.e. baseline) to be remeasured during and after an acute exacerbation after being stable again, with and without therapeutic interventions [15–17]. This will give an objective and real insight on the adverse effect of acute exacerbation(s) on the lung parenchyma through elastin degradation.

The current study revealed higher but non-significant values of blood DES level in current, compared to ex-smokers ($P > 0.05$) with non-significant correlation with the smoking index in the former patients' group (Table 2, Fig. 1). These results are in agreement with those of others [6,7], and they might reflect the fact that smoking causes COPD in a relatively small percentage of patients [18] i.e. who are susceptible to the deleterious effect of smoking causing significant lung parenchymal destruction with more elastinolysis and hence more DES and IDES production. The non-significant difference between current and ex-smokers could be explained by the persistence of chronic inflammation after abstaining from smoking in all but mild COPD patients. Linderberg et al. [19] demonstrated strong positive correlation between age and blood DES. In the current study the correlation was negative with statistically non-significant difference ($r = -0.1$, $P > 0.05$) (Table 4, Fig. 3) which may suggest decreased elastin turnover as part of the aging process.

Based on the results of the present study, it had been concluded that the blood level of desmosine was elevated in patients with stable COPD with further rise during acute exacerbations when compared to healthy control subjects. It can be speculated that the rise of blood desmosine level during acute exacerbation of COPD gives indirect evidence that these exacerbations could contribute to the severity of the disease by causing more and more lung destruction with progressive emphysematous changes and further deterioration of lung function.

Conflict of interest

No conflict of interest.

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